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EXAMINER	
O HARA, EILEEN B	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 02/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/978,188	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Eileen B. O'Hara	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 October 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *58-66 and 68-70* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *58-66 and 68-70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 October 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/28/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Status

1. Claims 58-66 and 68-70 are pending in the instant application. Claims 58-62 have been amended as requested by Applicant in the Amendment filed October 28, 2005.

Withdrawn Objections and Rejections

2.1 Any objection or rejection of record which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

2.2 Upon further consideration the rejections under 35 U.S.C. 102(b) and 35 U.S.C. 103(a) have been withdrawn, since this application is a direct continuation of 09/040,220, and is accorded an effective priority date of March 17, 1998.

Maintained Rejections

Claim Rejections - 35 USC § 101 and § 112

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

3. Claims 58-66 and 68-70 remain rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility, for reasons of record in the previous office actions, mailed May 19, 2004, and February 8, 2005, July 28, 2005, and below.

Applicants' arguments (pages 6-17, Paper filed October 28, 2005) have been fully considered but are not deemed persuasive.

Applicants traverse the rejection and discuss the legal standard for utility on beginning on page 8, and starting on page 11 discuss the proper application of the legal standard. Applicants rely on the gene amplification data for patentable utility for the PRO274 protein, and explain the gene amplification assay of Example 114, in which PRO274 is amplified 2.0 fold to 3.05-fold in three types of human primary lung tumors, which Applicants assert is significant and that the PRO274 gene has utility as a diagnostic of lung cancer.

The Examiner agrees with Applicants that the nucleic acids have utility as a diagnostic of lung cancer, however, the instant invention is drawn to polypeptides encoded by the nucleic acid, and because the art teaches that there is not necessarily a correlation between amplified genomic DNA and mRNA, or mRNA and encoded protein, the polypeptides do not have either a specific and substantial asserted utility or a well established utility.

Applicants at pages 8-9 refer to the Gygi et al. and Pennica et al. references. Applicants submit that the teachings of Pennica et al. are specific to WISP genes, and say nothing about the correlation of gene amplification and protein expression in general. Specifically, Pennica et al. (1998, PNAS USA 95:14717-14722), show a lack of correlation between gene amplification and overexpression in two out of three WISP genes. Hyman (Cancer Research 62:6240-6245, of record) found 44% of *highly* amplified genes showed overexpression at the mRNA level, and 10.5% of *highly* overexpressed genes were amplified; thus, even at the level of high amplification and high overexpression, the two do not correlate. Further, the article at page 6244 states that of the 12,000 transcripts analyzed, a set of 270 was identified in which overexpression

was attributable to gene amplification. This proportion is approximately 2%; the Examiner maintains that 2% does not provide a reasonable expectation that the slight amplification of PRO274 would be correlated with elevated levels of mRNA, much less protein. Hyman does not examine protein expression.

Applicants submit that Gygi et al. supports Applicants position that there is a positive correlation between mRNA levels and protein levels. While Gygi et al. demonstrates that high levels of mRNA generally correlate with high levels of protein and that it appears that there is a general positive correlation between mRNA levels and protein levels, it has not been demonstrated that the PRO274 mRNA is over-expressed. Given the small magnitude by which the DNA copy number of PRO274 is increased, and the evidence provided by Gygi et al. and Pennica et al., it is clear that one skilled in the art would not assume that a small increase in gene copy number would correlate with increased mRNA or polypeptide levels.

Applicant criticizes Chen et al. as not being applicable to the present application. Applicant asserts that Chen et al. only studied proteins detectable by 2D gels, and characterizes Haynes et al. as being critical of selecting proteins detectable by 2D gels, and quotes from Haynes et al. "It is apparent that without prior enrichment only a relatively small and highly selected population of long-lived, highly expressed proteins is observed. There are many more proteins in a given cell which are not visualized by such methods. Frequently it is the low abundance proteins that execute key regulatory functions" (Haynes, p. 1870, col. 1). This has been considered but not found persuasive. While Haynes et al. identifies limitations of this method of protein analysis, Haynes et al. also used the same method, 2D gels and mass spectrometry, to obtain their data, and discuss the advantages of this method. On page 1864,

second column, Haynes et al. states "There is considerable interest in developing a proteome analysis strategy which bypasses 2-DE altogether, because it is considered a relatively slow and tedious process, and because of the perceived difficulties in extracting proteins from the gel matrix for analysis. However, 2-DE as a starting point for proteome analysis has many advantages compared to other techniques available today. The most significant strengths of the 2-DE-MS approach include the relatively uniform behaviour of proteins in gels, the ability to quantify spots and the high resolution and simultaneous display of hundreds to thousands of proteins within a reasonable time frame." Haynes et al. on page 1870, first column, states "Comparative analysis of 2-DE protein patterns is therefore ideally suited for the detection, identification and analysis of suitable markers." And while Haynes et al. showed that there was a strong correlation between the most highly expressed proteins and mRNA levels using this same method, this was not the result in Chen et al. Chen et al. additionally did a detailed analysis of separate subsets of proteins with differing levels of abundance, and also showed a lack of correlation between mRNA and protein expression among the 165 protein spots (page 310, column 1).

Applicant also criticizes Chen et al. for looking at expression levels across a set of samples including a large number of samples (76) along with a much smaller number of normal samples (9), and for determining the relationship between mRNA and protein expression by using the average expression values for all samples, and therefore did not account for different expression in different tissues or different stages of cancer. This has been considered but not found persuasive. Applicant is holding Chen at al. to a higher standard than that of the instant application, in which there is no information on how many samples were tested, no information

about type or stage of tumor, no comparison with the equivalent normal tissue, and no information on protein level.

Thirdly, Applicants submit that no attempt was made to compare expression levels in normal versus tumor samples, and that the authors concede that they had too few samples for meaningful analysis (Chen, p.310, col. 2). Applicant asserts that as a result, the analysis in the Chen paper shows only that a number of randomly selected proteins have varying degrees of correlation between mRNA and protein expression levels within a set of different lung adenocarcinoma samples, and the Chen paper does not address the issue of whether increased mRNA levels in the tumor samples taken together as one group, as compared to the normal samples as a group, correlated with increased protein levels in tumor tissue versus normal tissue. This has been considered but not found persuasive. The section in Chen referred to did not refer to the entire sample, but addressed determining whether the 21 genes showing a significant correlation between the protein and mRNA expression among all samples demonstrate changes in this relationship during tumor progression, and the correlations were examined separately for stage I (n=57) and stage III (n=9) lung adenocarcinomas. The number of non-neoplastic lung samples (n=9) was insufficient for a separate correlation analysis of this group. Again, Applicant is holding Chen at al. to a higher standard than that of the instant application, in which there is no information on how many samples were tested, no information about type or stage of tumor, no comparison with the equivalent normal tissue, and no information on protein level.

Applicant asserts that the correct test of utility is whether the utility is "more likely than not", and assert that Chen et al. Table 1 shows that 40 genes out of 66 had a positive correlation between mRNA and protein expression, and that in Table II, 30 genes with multiple isoforms

were presented, in which for 22 out of 30, at least one isoform showed a positive correlation between mRNA expression and protein expression. Applicants submit that 12 genes out of 29 showed a strong positive correlation for at least one isoform, no genes showed a significant negative correlation, and certain isoforms are likely non-functional proteins. Thus, Table II also provides that it is more likely than not that protein levels will correlate with mRNA expression levels.

This has been considered but not found persuasive. In Table I, only 9 out of the 66 genes listed had a statistically significant positive correlation. For Table II, 19 out of 96 protein spots showed a statistically significant correlation between protein and mRNA expression. And though 12 genes out of 29 showed a strong positive correlation for at least one isoform, that is only 41%. Additionally, there is no information on which isoforms would be functional proteins and therefore no correlation between abundance of mRNA, protein level and functionality of protein.

Applicant submit the Beer et al. paper, having the same authors as in Chen et al., in which the authors look at several survival associated genes from lung adenocarcinoma, and report that the genes are expressed at the protein level and demonstrate similar mRNA and protein-expression patterns (page 822, col.1). Although the paper found a positive correlation between mRNA and protein expression, only 10 genes were analyzed. Additionally, these ten genes were selected for analysis because they were associated with survival and were highly expressed. The art indicates that highly expressed mRNAs correlate with high protein expression. However, there is no information in the instant application that the PRO274 mRNA is highly expressed. There are many papers that demonstrate no or little correlation, as

discussed above and below. A review of the literature indicates that some references demonstrate a positive correlation between mRNA expression and protein levels, while some show no correlation. From this, one of ordinary skill in the art would not assume that if an mRNA were differentially expressed, the protein would also be expressed in a corresponding manner.

Applicants further submit that the Orntoft, Hyman and Pollack references indicate that it is more likely than not that increased gene expression levels correlate with increased expression of the protein. This has been fully considered but is not found to be persuasive. Orntoft et al. (Molecular and Cellular Proteomics 1:37-45, 2002) could only compare the levels of about 40 well-resolved and focused *abundant* proteins." (See abstract.) It would appear that Applicants have provided no fact or evidence concerning a correlation between the specification's disclosure of *low* levels of amplification of DNA (which were not characterized on the basis of those in the Orntoft publication) and an associated rise in level of the encoded protein. Hyman (Cancer Research 62:6240-6245) found 44% of *highly* amplified genes showed overexpression at the mRNA level, and 10.5% of *highly* overexpressed genes were amplified; thus, even at the level of high amplification and high overexpression, the two do not correlate. Further, the article at page 6244 states that of the 12,000 transcripts analyzed, a set of 270 was identified in which overexpression was attributable to gene amplification. This proportion is approximately 2%; the Examiner maintains that 2% does not provide a reasonable expectation that the slight amplification of PRO274 would be correlated with elevated levels of mRNA, much less protein. Hyman does not examine protein expression. Pollack et al. is similarly limited to highly amplified genes which were not evaluated by the method of the instant specification. None of

the three references are directed to gene amplification, mRNA levels, or polypeptide levels in lung cancer.

Applicants submit on page 11-12 of the response that the teachings of Anderson et al. do not apply to the presently claimed invention because Anderson et al. studied mRNA/protein correlation in proteins obtained from liver tissue, while the present invention is directed to polypeptides that are overexpressed in lung tumor, which is an entirely different cellular environment from liver tissue, and it would be apparent that different post-translational or post-transcriptional regulation mechanisms are involved in these two systems. Applicants' arguments have been fully considered but are not deemed persuasive. Applicants have presented no evidence that the post-translational or post-transcriptional regulation mechanisms differ from lung tumor and liver tissue. Additionally, Applicants use Gygi et al. to support their position, but the data in Gygi et al. was obtained from yeast, which one of ordinary skill in the art would consider far more different from lung tumor than liver cells. Applicants further submit that Anderson admitted that several experimental flaws in this paper will limit the accuracy of the data. Anderson et al. addresses this on page 536, right column, and states:

"Although the measurements obtained show good (1ow) standard deviations across a set of six individual livers, it is well known that different proteins can bind CBB with different affinities. Thus the measurement scale for one protein may differ from another by up to approximately twofold. Since, however, these relative scale errors should be normally distributed, we expect them to have little effect on the overall correlation. Precision of the mRNA measurements is also limited, in this case because a limited number of clones was detected for the selected proteins. Five genes, for example, were represented by only one clone each among the 7925 clones sequenced from the respective CDNA tissue libraries. This low relative expression at the mRNA level is expected since a majority of the high abundance mRNAS in liver code for plasma

proteins. However, such small numbers of clones lead to potentially large quantitative errors because of sampling error. Here again, we believe these errors should be relatively random across the set of proteins chosen, and thus should not skew the result appreciably. A third potential difficulty is that the databases used for the protein and mRNA abundance estimates were prepared from different samples. In future, it will thus be of great interest to repeat the experiment using the same samples to examine both mRNA and protein abundances."

Therefore, Anderson et al. believe their data is relatively accurate. Applicants further submit that Anderson et al. supports their position by showing a correlation of 0.48. Anderson et al. address this on page 536, right hand column:

"Matches were found for 19 proteins, and the correlation coefficient obtained over this set of data was 0.48. This number is intriguingly close to the middle position between a perfect correlation (1.0) and no correlation whatever (0.0). One simple interpretation of such a value is that the two major phases of gene expression regulation (transcription through message degradation on the one hand, and translation through protein degradation on the other) are of approximately equal importance in determining the net output of functional gene product (protein)."

Though Anderson et al. found some correlation with this data set, they reanalyzed an analogous set of data for plasma proteins secreted by the liver published by Kawamoto et al. On page 536, left column, Anderson et al. states:

"An analogous set of data for plasma proteins secreted by the liver has been published by Kawamoto et al. [12] and we have reanalyzed their values to see whether a similar mRNA-to-protein relationship holds. It appears, based on nine plasma proteins, that a higher correlation coeflicient applies: 0.96. Thisis result is less convincing, however, because one gene product (albumin) is well-separated from the cluster of the remaining eight, and thus exercises a disproportionate influence on the correlation coefficient. In fact, if albumin is omitted from the

calculation, the correlation coefficient is reduced to -0.19, which suggests a very poor correlation."

Therefore, from the Anderson et al. paper alone, one of ordinary skill in the art would not assume that if an mRNA were overexpressed, the protein would correspondingly be overexpressed.

Applicants reiterate that the evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration. Applicants submit that the Office has failed to meet its initial burden of proof that Applicant's claims of utility are not substantial or credible, and that the arguments presented by the Examiner in combination with the Chen et al. and Anderson et al. papers do not provide sufficient reasons to doubt the statements by Applicants that PRO274 has utility, and that the papers support Applicant's position. Applicants' arguments have been fully considered but are not deemed persuasive, for the reasons discussed above. While the credibility of the utility is not in doubt, the asserted utility is not considered substantial.

Additional references show lack of correlation between mRNA levels and protein levels. Lian et al., (2001, Blood 98:513-524) show a lack of correlation between mRNA expression and protein expression in mouse cells (see p. 514, top of left column: "The results suggest a poor correlation between mRNA expression and protein abundance, indicating that it may be difficult to extrapolate directly from individual mRNA changes to corresponding ones in protein levels."). See also Fessler et al., (2002, J. Biol. Chem. 277:31291-31302) who found a"[p]oor concordance between mRNA transcript and protein expression changes" in human cells (p. 31291, abstract). The evidence as a whole clearly indicates that one skilled in the art would not assume that an increase in mRNA levels results in increased protein levels without doing the empirical

experimentation necessary to measure protein levels. The requirement for such empirical experimentation indicates that the asserted utility for the claimed polypeptides is not substantial; it is not in currently available form.

At pages 13-15 of the response, Applicant refers to Ornoft et al., Hyman et al., and Pollack et al. as evidence supporting the assertion that gene amplification more likely than not correlates with increased polypeptide levels. Applicant characterizes Ornoft et al. as studying transcript levels of 1,800 genes in two invasive tumors compared to two non-invasive papillomas, many of which were linked to the gain or loss of chromosomal material and found that in general (77% and 80% condordance) chromosomal areas with a strong gain of DNA showed a corresponding increase in mRNA transcripts. Applicants also submit that Ornoft et al. found a high correlation between alter mRNA levels and protein levels.

This has been fully considered but is not found to be persuasive. Ornoft et al. (Molecular and Cellular Proteomics 1:37-45, 2002) could only compare the levels of about 40 well-resolved and focused *abundant* proteins." (See abstract.) It would appear that Applicants have provided no fact or evidence concerning a correlation between the specification's disclosure of *low* levels of amplification of DNA (which were not characterized on the basis of those in the Ornoft publication) and an associated rise in level of the encoded protein.

Applicant characterizes Hyman et al. as finding a "clinical association between HOXB7 amplification and poor patient prognosis, thus confirming that genes which are amplified in tumors have prognostic utility. Applicants' arguments have been fully considered but are not deemed persuasive. It is not disputed that amplified genes in at least one type of tumor are

useful as markers for that type of tumor. However, amplification of a gene does not necessarily correlate with increased mRNA or protein.

Applicants submit that the articles by Orntoft et al., Hyman et al., and Pollack et al. were submitted as evidence that, in general, gene amplification increases mRNA expression, and further submitted the Declaration of Dr. Paul Polakis as evidence that, in general, there is a correlation between mRNA levels and polypeptide levels. In the declaration, Dr. Polakis states that the primary focus of the Tumor Antigen Project was to identify tumor cell markers useful as targets for cancer diagnostics and therapeutics. Dr. Polakis states that approximately 200 gene transcripts were identified that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. Dr. Polakis states that antibodies to approximately 30 of the tumor antigen polypeptides have been developed and used to show that approximately 80% of the samples show correlation between increased mRNA levels and changes in polypeptide levels. Applicants submit that while the proper legal standard is to show that the existence of correlation between mRNA and polypeptide levels is more likely than not, the showing of approximately 80% correlation for the molecules tested according to the Polakis Declaration greatly exceeds this legal standard. Dr. Polakis confirms that "it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein." This has been fully considered but is not found to be persuasive. The declaration does not provide data such that the examiner can independently draw conclusions. Only Dr. Polakis' conclusions are provided in the declaration. There is no evidentiary support to Dr. Polakis' statement that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the

encoded polypeptide. Finally, it is noted that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue (Hu et al., of record).

In addressing the argument that only transcripts that are present in tumor cells at significantly higher levels than in corresponding normal human cells were analyzed, Applicants submit that they have already shown that, as evidenced by the Goddard Declaration, the gene encoding PRO274 showed significant amplification in lung tumors compared to normal tissues.

This has been fully considered but is not found to be persuasive. In assessing the weight to be given expert testimony, the examiner may properly consider, among other things, the nature of the fact sought to be established, the strength of any opposing evidence, the interest of the expert in the outcome of the case, and the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993). In the instant situation, the nature of the fact sought to be established is whether or not a 2.0 fold to 3.05-fold fold amplification of the gene encoding PRO274 would result in increase mRNA and protein levels. It remains that, as evidenced by Gygi, Pennica, Chen, Anderson, Lian and Fessler, the issue is simply not predictable, and the specification presents a mere invitation to experiment. Based on consideration of the evidence as a whole, the rejection is proper.

Applicants submit that taken together, although there are some examples in the scientific art that do not fit within the central dogma of molecular biology that there is a correlation between DNA, mRNA and polypeptide levels, these are exceptions rather than the rule.

Applicants' arguments have been fully considered but are not deemed persuasive. From the totality of the evidence, it is not predictable that PRO274 protein levels would be increased in cancer and would be diagnostic of such.

Applicants further assert that even if gene amplification does not result in over-expression of the protein, an analysis of the expression of the protein is useful in determining the course of treatment, as indicated by Dr. Ashkenazi in his Declaration and the teachings of Hanna (Mornin was not submitted by Applicants). Applicants submit that simultaneously testing of gene amplification and gene product over-expression enables more accurate tumor classification, even if the protein is not over-expressed, which leads to a better determination of a suitable therapy for the tumor as demonstrated by the real-world example of the breast cancer marker HER-2/neu.

Applicants' arguments have been fully considered but are not deemed persuasive. It has not been demonstrated that the protein of the instant invention is differentially expressed in different tumors. If it was, the protein would have a specific and substantial utility for tumor classification, but the mere assertion that it may be differentially expressed does not provide a specific and substantial utility, and is an invitation to experiment.

One skilled in the art would do further research to determine whether or not the PRO274 polypeptide levels increased significantly in the tumor samples. The requirement for such further research requirements makes it clear that the asserted utility is not yet in currently available form, i.e., it is not substantial. This further experimentation is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete. The

instant situation is directly analogous to that which was addressed in *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sus. Ct, 1966), in which the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

The proposed uses of the claimed invention are simply starting points for further research and investigation into potential practical uses of the claimed polypeptides. For all of these reasons, the rejections are maintained.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4.1 Claims 58-66 and 68-70 also remain rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

4.2 Claims 58-62 and 69-70 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for reasons of record in the office actions mailed May 19, 2004, February 8, 2005, July 28, 2005, and below.

Applicants traverse the rejection on pages 17-20 and assert that the polypeptide comprising the sequence set forth in SEQ ID NO: 7 meets the written description requirement of 35 U.S.C. 112, first paragraph, and thus the genus of polypeptides with at least 80% sequence identity to SEQ ID NO: 7, which possess the functional property of having a nucleic acid which is amplified in lung tumors would meet the requirement of 35 U.S.C. 112, first paragraph, as providing adequate written description. Applicants assert that the present application also describes methods for identifying genes which are amplified in lung cancer, and that by following the disclosure in the specification, one skilled in the art can easily test whether a gene encoding a variant PRO274 protein is amplified in lung cancer, and also the specification further describes methods for the determination of percent identity between two amino acid sequences.

Applicants assert that an applicant may also show that an invention is complete by disclosure of sufficiently detailed relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. Applicants submit that they have recited structural features, namely, 80% sequence identity to the genus of claimed polypeptides is further defined by having a specific functional activity for the encoding nucleic acid, of being amplified in lung tumors. Applicants also direct the Examiner's attention Example 14 of the Synopsis of Application of Written Description Guidelines issued by the U.S. Patent Office, which clearly states that protein variants meet the requirements of 35 U.S.C. 112, first paragraph, as providing adequate written description for the claimed invention even if the specification contemplates but does pot

exemplify variants of the protein if (1) the procedures for making such variant proteins are routine in the art, (2) the specification provides an assay for detecting the functional activity of the protein and (3) the variant proteins possess the specified functional activity and at least 95% (80%) sequence identity to the reference sequence.

Applicants' arguments have been fully considered but are not deemed persuasive. In this case, the only factors present in the claim are functional, in that the protein of SEQ ID NO: 7 is encoded by a nucleic acid that is amplified in lung cancer. The specification discloses only a single sequence, SEQ ID NO: 7, that meets the limitations of the claims. It is clear that while there *could* be additional polypeptides that meet the limitations of the claims, that conception of such polypeptides has not occurred, and cannot occur until their actual isolation, as it is not predictable what additional mutations in SEQ ID NO: 7 would occur in nature and further be amplified in lung cancer. As previously stated, one cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQZII 1481 at 1483. In *Fiddes,* claims directed to mammalian FGF'S were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence. In this case, applicants have described a single sequence asserted to be associated with lung cancer, and propose to obtain coverage for all related sequences that have a similar association. There is no description of that class of compounds. This case is also analogous to that in *Amgen v. Chugai*, 18 USPQ 2d 1017 (1991), in which it was found that conception may not be achieved until reduction to practice in cases involving cloning genes. In this case, applicants have no conception of which of the thousands of possible polypeptides and nucleic acids that could encode the protein of SEQ ID NO: 7 would meet the limitation of being amplified in lung cancer.

Vas-cath Inc. v. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. Chugai Pharmaceutical Co. L td.*, 18 USPQ2d 1016.

Therefore, polypeptides comprising the sequence set forth in SEQ ID NO: 7, but not the full breadth of the claims meet the written description provision of 35 U.S.C. § 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision (see page 1115).

It is believed that all pertinent arguments have been answered.

Conclusion

5. No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara, whose telephone number is (571) 272-0878. The examiner can normally be reached on Monday through Friday from 10:00 AM to 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached at (571) 272-0961.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://portal.uspto.gov/external/portal/pair. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Eileen B. O'Hara, Ph.D.

Patent Examiner

EILEEN B. O'HARA
PATENT EXAMINER